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Systemic lupus erythematosus

Measures to keep this unpredictable disease under control

Brent Greenberg, MD; Margaret Michalska, MD

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POSTGRADUATE MEDICINE**

CME learning objectives

- To recognize common signs and symptoms of SLE
- To become familiar with criteria established by the American College of Rheumatology as the basis for diagnosis
- To identify appropriate treatment and preventive measures

This page is best viewed with a browser that supports tables

Preview: Systemic lupus erythematosus can present in many ways, often mimicking other diseases. In this article, Drs Greenberg and Michalska describe the numerous manifestations of this autoimmune disease, the widely accepted criteria for diagnosis, and the therapeutic measures that can prolong survival and decrease morbidity. *Greenberg B, Michalska M. Systemic lupus erythematosus: measures to keep this unpredictable disease under control. Postgrad Med 1999;106(6):213-23*

Systemic lupus erythematosus (SLE) is frustrating to the medical community and patients alike. The cause of this autoimmune disease is unknown, and nearly all of its clinical features are seen in other diseases as well. Further, the classic malar rash specific to SLE occurs in less than half of SLE patients, and diagnostic tests touted over the past half century have shown crossover with other autoimmune diseases (1). However, certain clinical and laboratory criteria may point strongly to SLE and enable the selection of appropriate treatment.

Who is at risk

SLE can occur at any age but is most often a disease of women in their childbearing years. Although incidence peaks between ages 15 and 40 years, as many as 40% of cases may present initially after age 60. SLE affects 1 in 3,000 persons in the United States, striking women five to nine times more often than men. US statistics show the disease to be more prevalent in African American and Hispanic women than in white women,

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but this finding may be influenced by socioeconomic factors (2).

A familial correlation exists, especially in first-degree relatives. Coexisting autoimmune diseases such as rheumatoid arthritis and idiopathic thrombocytopenic purpura may be seen in other family members.

Despite hereditary influence, most cases of SLE are idiopathic (2). Environmental factors may play a role, as suggested by a study showing that dogs belonging to patients with a new diagnosis of SLE had a higher frequency of anti-DNA antibodies than dogs belonging to subjects in the general population (3).

What causes SLE

Lupus is a chronic inflammatory disease of unknown origin. It is characterized by the body's production of antibodies to nuclear components of the cell. Whether it is a single condition or a group of related diseases is not known. The cutaneous form of SLE that is confined to the integument (discoid SLE) may be distinguished from the systemic form.

Pathogenesis is likely multifactorial. Genetically predispositioned immunologic influences, such as associations with HLA class II alleles DR2 and DR3, play a role, along with complement deficiencies (primarily C3a and C4b) and ethnic susceptibilities (4). Homozygous C4a deficiency is associated with a high risk for SLE. This deficiency has been postulated to increase the risk for impaired clearance of foreign antigen, and this could thereby stimulate the immune system, leading to a chronic inflammatory response.

Viral and bacterial antigens have long been thought to be a possible source of SLE, but no pathogen has been consistently determined. Certain medications and environmental exposures have been found to create or exacerbate SLE symptoms.

Prognosis

Forty years ago, most people with SLE survived less than 5 years. Changes in diagnosis and treatment have improved survival to the point where more than 90% of patients now survive for more than 10 years (5). Most live a relatively asymptomatic life.

The most common cause of death is infection resulting from the immunosuppressive side effects of medications used to treat the disease. Renal and neurologic manifestations cause the greatest morbidity and are associated with a worse prognosis than other manifestations (1). Overall, prognosis is usually worse in men and children than in women. Life-threatening complications are most common in the first 5 years of manifestations. Symptoms that begin after age 60 tend to run a more benign course.

Symptoms and signs of SLE

In 1895, Sir William Osler described SLE in this manner (6):

By exudative erythema is understood a disease of unknown etiology with polymorphic skin lesions—hyperemia, edema, and papules, nodules, vesicles, and . . . vesicular manifestations of which the characteristic spots, erythematous, and hemorrhagic from the mucous surfaces. Recurrence is a special feature. . . . and attacks may come on month after month or even throughout a long period of years.

Osler's observations, compiled without the benefit of powerful laboratory tools, still provide an accurate picture of SLE, as discussed in the following sections.

Constitutional signs and symptoms

Common renal and chronic complaints are fever, malaise, myalgias, and weight loss. Because they are so often seen with other diseases, these signs and symptoms are not part of the diagnostic criteria for SLE. However, when they occur in isolation, these signs and symptoms, they should be considered suggestive. Fatigue is often a nonspecific, unremitting condition in SLE, but worsening fatigue may reflect a lupus flare.

Musculoskeletal conditions

Arthritis is the most common reason patients with SLE seek medical attention. Small joints of the hand and wrist usually are affected. Swollen in a migratory presentation, but any joint is at risk. Soft-tissue and tendon thickening causes swelling that involves little of the joint; therefore, effusions, if any, are small.

Unlike rheumatoid arthritis, SLE arthropathy is usually not erosive or destructive to bone. Patients may complain of morning stiffness, but with few physical findings. However, deformities may become irreversible. Jaccoud's arthropathy, with attendant ligamentous laxity, subluxations, and tendon ruptures, may develop in as many as 20% (7).

Dermatologic manifestations

Skin manifestations are second only to arthralgias in frequency. As many as 20% of patients present with dermatologic symptoms (and 65% manifest such symptoms at some point) secondary to destruction of the skin by deposition of immune complexes in the dermal-epidermal junction (8). In 30% to 50% of patients, malar rash develops after sunlight exposure. This may be a pruritic or painful erythematous flat patch or raised plaque over malar eminences, sparing nasolabial folds.

Subacute cutaneous lupus erythematosus is a distinct, nonscarring, sometimes coin-shaped lesion that occurs over sun-exposed areas and mimics psoriasis. Patients often demonstrate the antiSS-A (Ro) antibody (3).

Discoid lesions are often considered a separate entity, existing without systemic manifestations. Chronic lesions begin as thick, scaling, adherent plaques with central hypopigmentation and atrophy. In about 10% of patients, these lesions progress to SLE (5). Alopecia, painless oral lesions, vaginal ulcers, and vascular lesions such as palpable purpura and splinter hemorrhages are all possible manifestations.

Vasculopathy

Arterial and venous thrombosis is a sequel to chronic inflammatory events triggered by autoantibodies. Anticardiolipin and lupus anticoagulant antibodies are the most common serologic findings, but their mechanisms are unknown. Vascular lesions may occur in the form of petechiae, purpura, or ecthymoses in the skin or swollen tendons in the joints. Ischemic, tender nodules. Seizures, strokes, or behavioral changes may ensue if the cerebral vessels are affected. Renal and coronary arteries are rarely involved (5).

Renal involvement

Because of early recognition and aggressive management of SLE, renal symptoms are rarely a problem until advanced disease may be in motion or renal failure develops. Painless hematuria or proteinuria may be the only or the first presenting symptom. Renal disease develops in about 35% of patients, but end-stage renal failure occurs in less than 5% (3).

Urinalysis alone is not useful for prognosis. Kidney biopsy is the most reliable indicator of the type and severity of disease. The primary reason for performing biopsy is to determine the type of glomerulonephropathy or to investigate the cause of atypical renal failure (9).

Cardiac symptoms

Pericarditis, myocarditis, and endocarditis can occur from nonspecific inflammation. Libman-Sacks or verrucous lesions are not uncommon. Corticosteroids became available for treatment. However, these lesions can manifest as immune complexes on the mitral valve, where bacteria can accumulate. Lesions, even when clinically silent, are found in more than half of autopsies. Atherosclerosis tends to occur more often (3:1 ratio) and to advance more rapidly in patients with SLE than in the general population.

Thus, these patients are at increased risk for myocardial infarction (9).

Serologic features

Leukopenia, pericarditis, and peritonitis are common features of SLE. Pleural effusions, pericardial effusions, and ascites can be large. The fluid often contains antinuclear antibodies (ANAs), low complement, and immune complexes.

Hematologic manifestations

Anemia secondary to chronic inflammation, iron deficiency, and hemolysis may develop in as many as half of SLE patients. Thrombocytopenia and leukopenia may be due to SLE or to side effects of pharmacologic treatment.

Neurologic symptoms

About 10% of patients with SLE may have a neuropsychiatric manifestation as the presenting symptom. A third may have positive findings on neuroimaging, but the results are nonspecific. Functional MRI and PET scan focal areas of increased signal intensity. Electroencephalography and gallium scans have not shown any diagnostic value. Computed tomography may be useful for viewing infarcts (9).

Diagnostics of SLE

The American College of Rheumatology has delineated criteria for the diagnosis of SLE. Various laboratory tests, when considered in conjunction with clinical findings, point to the diagnosis.

Diagnostic criteria

In 1982 the American College of Rheumatology revised their criteria for diagnosis of SLE (table 1; not shown). Four of their 11 criteria must be met, either together or at different times. These criteria are widely accepted for use in clinical trials and to guide therapy.

Laboratory tests

The lupus erythematosus cell preparation (LE cell prep) test was devised almost 50 years ago as the first laboratory test for diagnosis of SLE. Since its inception, this test has been found to have sensitivity of only 50% and specificity of 40% as an adjunct. This test prompted research into proteins that act like antibodies but respond to normal cells.

Today, the ANA test is the mainstay in diagnosis of SLE. This test has high sensitivity but poor specificity. A test using fixed and permeabilized human Hep-2 cells measures binding of the patient's serum antibodies to the cell nucleus (10). Antinuclear antibodies are found in more than 90% of patients at some time. The false-positive rate for this test is 1% to 2% in patients with age. High titers are seen in 95% of active flares and in 50% of patients with age. High titers are seen in 95% of active flares and in 50% of patients with age. High titers are seen in 95% of active flares and in 50% of patients with age.

The immunofluorescent patterns of antibody distribution correlate with certain autoimmune disease states. Malarial, homogeneous, and speckled patterns are seen in various states. Homogeneous, speckled, and peripheral, or rim, pattern is the most specific to SLE. Although the commonly seen (11). Subtypes of nuclear proteins have been found to overlap with other rheumatologic diseases, but antibodies to double-stranded DNA (anti-dsDNA) and to an RNA protein complex (anti-Sm) have been found to be most diagnostic of SLE.

When autoimmune flares occur, complement factors are consumed. Low complement levels, particularly C3 and C4, have also been used as important measures. Among SLE patients, 11% have an inherited complement defect (9). Although ANA titers, subtypes, patterns, and complement levels are useful in diagnosis, they are inconsistent in following flares. These levels may rise a year or more before clinical disease flares. Anti-dsDNA may be seen 30% to 50% of the time, while anti-Sm may be seen 30% to 50% of the time (2). Immunologic markers can be useful but should be interpreted for assessment of clinical manifestations when guiding a treatment plan.

Urinalysis demonstrating hematuria (>5 red blood cells per high-power field), presence of any casts, pyuria (>5 white blood cells per high-power

field) in the absence of infection, and proteinuria (>0.5 g/dL or +3 on dipstick) may indicate renal involvement. In the context of other clinical signs, these findings warrant a renal workup.

Leukocytes, primarily polymorphonuclear neutrophils, are often decreased during a flare. This occurs because leukocytes bind to complement receptors, creating a cascade release of proteolytic enzymes that perpetuate inflammation and adhere to vascular endothelium, possibly leading to the occlusion of small blood vessels. Autoantibodies bind to platelets, causing thrombocytopenia. Autoantibodies may also bind to erythrocytes or bleeding from the gums, which is a hematological tract. Unlike in idiopathic thrombocytopenic purpura, splenectomy is rarely necessary.

Cerebrospinal fluid findings emulate those of aseptic meningitis. Increased protein levels and pleocytosis are found in 50% of patients.

A false-positive rapid plasma reagin test may occur in conjunction with a negative fluorescent treponemal antibody absorption test. These findings often correlate with a positive lupus anticoagulant or antiphospholipid antibody test.

In small-joint effusions, a high percentage of polymorphonuclear neutrophils without a concomitant infection or decreased complement levels is often seen.

The erythrocyte sedimentation rate can be high, but this occurs too inconsistently to be useful in diagnosing SLE or monitoring flare progression.

Special cases of SLE

Because of the complexity of SLE, some special cases must be noted that have a different pathogenesis and course:

Pregnancy in SLE patients

Fertility rates in women with SLE match those in the general population. However, half the pregnancies in these women result in premature birth or stillbirths. About 10% of pregnancies in these women result in miscarriage. Constitutional symptoms and signs of the disease may be more common, occurring most often early in the pregnancy. Many patients manifest symptoms that may be indistinguishable from preeclampsia (7,12).

Prothionic, nonsteroidal antiinflammatory drugs (NSAIDs), and most other medications for treating lupus symptoms are contraindicated in pregnancy. Hydroxychloroquine (Plaquenil) sulfate and azathioprine (Imuran) under investigation for their safety. Cyclophosphamide (Cytoxan, Neosar) and methotrexate (Folex, Rheumatrex) are contraindicated in pregnancy.

Neonatal lupus

A third of mothers with SLE carry the antiSS-A (Ro) antibody. 10% of these will give birth to a baby with neonatal lupus. The most common symptoms are rash, transient anemia and, rarely, complete heart block. Except for the cardiac manifestations, the illness is typically transient and resolves by the age of 3 to 6 months (2).

Drug-induced lupus

In 1945, the first lupuslike reaction to a medication was reported with sulfasalazine (Azulfidine). Since then, 70 drugs have been implicated as causing or exacerbating SLE. Many of these are listed in table 2. Drug-induced lupus is most frequent in older patients. Men and women are equally at risk. The most common symptoms are fever, fatigue, arthralgia, and serositis.

Table 2. Medications that may cause drug-induced lupus

Atenolol (Tenormin)
Captopril (Capoten)

Carbamazepine
Chlorpromazine HCl (Thorazine)
Clonidine HCl (Catapres)
Danazol (Danocrine)
Daclofenac (Cataflam, Voltaren)
Disopyramide (Norpace)
Ethosuximide (Zarontin)
Gold compounds
Griseofulvin
Hydralazine HCl (Apresoline)
Ibuprofen
Imipramine HCl (Tofranil)
Isometolol (Lanazid, Hydrazid)
Labetalol HCl (Normodyne, Trandate)
Leuprolide acetate (Lupron)
Levodopa (Dopar, Larodopa)
Lithium carbonate
Lovastatin (Mevacor)
Meprobamate (Meprodon)
Methyldopa (Aldomet)
Methysergide maleate (Serpent)
Minoxidil (Loniten)
Nalidixic acid (Neogran)
Nitrofurantoin (Furadantin)
Nitroglycerin (Nitrostat)
Oral contraceptives
Penicillamine (Cuprimine, Depen)
Penicillin
Phenelzine sulfate (Nardil)
Phenytoin sodium (Dilantin)
Prazosin (Minipress)
Procainamide HCl (Procan, Provent)
Propylthiouracil
Psoralen
Quinine
Spironolactone (Aldactone)
Streptomycin sulfate
Sulfadiazine (Cintrol)
Sulfasalazine (Azulfidine)
Tetracycline
Thiazide HCl (Melectin)
Timolol maleate (Betimol, Timoptic)
Tolazamide (Tolinase)
Tolmetin sodium (Tolmetin)
Trimethadione (Tridione)

Adapted from Callaghan and Williams (10).

The drugs most commonly associated with lupuslike flares include procainamide hydrochloride (Procan, Proventyl), hydroxychloroquine (Aprelone), and isoniazid (Lanazid, Hydrazid). Symptoms develop in about 30% of patients who take procainamide for more than a year. In patients taking hydralazine, symptoms are unlikely to occur at dosages of 200 mg/day or less.

There is no consensus on diagnostic criteria for drug-induced lupus, but it should be suspected in patients who have significant ANA titers and constitutional symptoms. These findings occur in more than 95% of patients with drug-induced lupus (3). Usually all symptoms resolve after use of the drug is discontinued. Laboratory findings may persist for up to a year after symptoms resolve.

Treatment

SLE is a chronic disease that waxes and wanes. Treatment is focused on medication to control the disease and measures to prevent flares. Management is based on the degree and severity of problems. The presence of acute confusional states or fatigue should also guide

management. The measures discussed here have been shown to prolong survival and decrease morbidity.

Medications
The medications discussed here may be used alone or with other agents. Combined use may allow lower doses of each and decrease the risk of side effects.

NSAIDs treat constitutional symptoms of fatigue, musculo-skeletal pain, and serositis. Response is variable, and no one particular NSAID has proved to be better than another. Adverse effects include reversible gastrointestinal and renal impairment, confusion, and dizziness.

Corticosteroids have many uses in SLE. Topical preparations are used for rashes, intralesional injections for discoid rash, low oral doses for mild symptoms, and high oral or intravenous doses for severe symptoms. The type of steroid used is less important than the dose. High doses should not be given for more than a month. Tapering is essential to prevent relapse and hypothalamic-pituitary-adrenal crisis. A threshold dose, where activity is predictable, can usually be established.

Hydroxychloroquine was originally used to treat malaria and later found to be useful in rheumatoid arthritis. It alleviates cutaneous, musculoskeletal, and constitutional symptoms. Improvement occurs over a matter of days to weeks. Patients can benefit by remaining on a prophylactic dose indefinitely. Side effects include gastrointestinal symptoms, pigment changes, and retinal damage. If acute neurologic symptoms develop, the medication should be stopped. Retinal damage is detected by fundus examination and should be performed before the drug is given and at regular follow-ups.

Azathioprine is used as a second-line steroid-sparing agent to control renal disease and prevent premature. Major side effects include bone marrow suppression. Frequent complete blood cell counts are mandatory. There may also be increased risk for certain hematopoietic cancers with use of this medication.

Cyclophosphamide is a medication of last resort to manage progressive renal disease and decrease risk of end-stage renal failure. It is used also to treat hypogonadism and severe rheumatologic symptoms. This drug is contraindicated in pregnancy. It also increases risk for bladder damage.

Methotrexate may be used as a second-line agent for treating SLE-related arthritis and rashes. Dexamethasone (Dexamone), an attenuated androgen, may be useful for severe and refractory alopecia, although its mechanism is unclear. Gamma globulins have shown effects on renal, hematologic, and neuropsychiatric symptoms, but the relapse rate is high. Plasmapheresis has only transient effects, and it, too, has a high relapse rate. Research efforts are being focused on modified combination regimens to decrease side effects.

Prevention of flares
SLE symptoms can be controlled to a certain degree with preventive measures. By avoiding intense sun exposure, patients can prevent burns, which release antibodies to DNA and exacerbate rashes (1). When outside, they should wear sunscreen, a large-brimmed hat, and long-sleeved clothing. Persons with SLE should avoid outdoor occupations and photosensitizing medications.

Aggressive treatment of infections is paramount, since infection is a major cause of morbidity and mortality. Fever without a source must be thoroughly evaluated and treated. Annual inoculation with influenza vaccine is imperative. Antibiotic prophylaxis should be considered for all dental and surgical procedures. Most infections are treatable, but sulfonamide drugs should be avoided because they increase photosensitivity.

Contraception with low-dose estrogen or progestin is probably safe unless a patient has a history of thrombotic events, liver disease, or antiphospholipid antibody syndrome. Obstetric care should be managed by a perinatal specialist, because immunosuppressants entail a risk for infertility, sperm and ova banking should be discussed.

By providing educational materials and information about support networks, physicians can help patients achieve and maintain control over their symptoms, enabling them to minimize flares and live functional, productive lives with this chronic illness.

Summary

SLE is a chronic autoimmune disease with an unpredictable history and course. It can occur in men or women at any age, but it is most prevalent in women of childbearing age. SLE displays a variety of clinical and laboratory manifestations that vary from vague constitutional symptoms to findings of end-organ dysfunction. Early diagnosis and aggressive treatment and preventive care, thereby reducing the risk of severe organ, cardiovascular, and septic manifestations. Recognition and management of lupus flares and of medication side effects can markedly reduce morbidity and mortality, allowing patients to live more functional lives.

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A brief history of lupus

The 13th century physician Rogerius coined the term "lupus" (Latin for "wolf") to describe facial lesions resembling a wolf's bite. The French physician Cazenave later termed the reddish complexion on young female faces lupus erythematosus. In 1845, Von Hebra described the rash as having a butterfly appearance. Thirty years later, Kaposi described more of the disease's clinical components (1). Near the turn of the century, Osler (2) distinguished the acute and chronic forms of the disease. Klemperer coined the term "collagen vascular disease," the major mutations in the collagenous components of fibrous connective tissue associated with systemic lupus erythematosus and other autoimmune diseases.

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INFORMATION FOR PATIENTS

Where to find information about SLE

Support groups exist nationwide, sponsored by the Lupus Foundation of America. A Web site lupus home page by Hamline University, St Paul, Minnesota, provides information on all aspects of the disease, including symptoms, treatment, support groups, research, and breakthroughs in the field. The site is available at <http://www.hamline.edu/lupus>.

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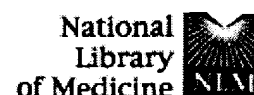
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Evaluation of soluble tumor necrosis factor (TNF) receptors and TNF receptor antibodies in patients with systemic lupus erythematoses, progressive systemic sclerosis, and mixed connective tissue disease.

Heilig B, Fiehn C, Brockhaus M, Gallati H, Pezzutto A, Hunstein W.

Medizinische Klinik und Poliklinik V, Universitat Heidelberg, Germany.

Two TNF binding proteins have been characterized as soluble fragments of TNF receptors. We measured the plasma concentrations of soluble type A (p75) and type B (p55) TNF receptors in patients with systemic lupus erythematoses (SLE), progressive systemic sclerosis (PSS), and mixed connective tissue disease (MCTD). In SLE and PSS patients plasma concentrations of both types of TNF receptors and in MCTD patients type A TNF receptors were significantly elevated compared to controls. Plasma concentrations of both soluble TNF receptors were highly correlated in SLE, PSS, and MCTD patients, indicating a possible coregulation of both TNF receptors. In contrast, soluble interleukin 2 receptor (sCD 25) plasma concentrations were not correlated and seem to be an independent parameter. The soluble forms of the TNF receptors neutralize TNF in cytotoxicity assays and are functionally active as TNF antagonists. In one patient with SLE, autoantibodies against type A TNF receptors were detected, TNF alpha, and TNF beta did not interfere with the autoantibody binding to the receptor.

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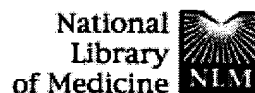
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The role of the 16/6 idiotype network in the induction and manifestations systemic lupus erythematosus.

Waisman A, Mendlovic S, Ruiz PJ, Zinger H, Meshorer A, Mozes E.

Department of Chemical Immunology, Weizmann Institute of Science, Rehovot, Israel.

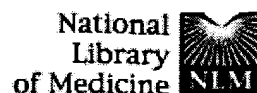
Experimental systemic lupus erythematosus (SLE) has been induced in mice by immunization with either a human anti-DNA mAb bearing a common idiotype (Id) designated 16/6 Id (antibody 1, Ab1) or with a murine anti-16/6 Id mAb (Ab2). In the present study a murine mAb (5G12-4, Ab3) that bears the 16/6 Id and binds to DNA was produced and was found to bind rabbit anti-16/6 Id sera and murine anti-16/6 Id mAb similarly to the human mAb 16/6 Id (Ab1). Moreover, mAb 5G12-4 was shown to share cell epitopes with the human 16/6 Id mAb, since lymph node cells of mice immunized with the mAb 5G12-4 proliferated significantly to the human 16/6 mAb and vice versa. Following immunization of mice with the murine mAb bearing the 16/6 Id, antibodies to dsDNA, ssDNA, 16/6 Id, anti-16/6 Id, and to HeLa nuclear extract proteins were detected similarly to those observed previously upon immunization with Ab1 or Ab2. Six months following the immunization, the mice exhibited leukopenia, increased erythrocyte sedimentation rates, and proteinuria. Examination of the kidneys of the mice disclosed immune complex deposits, thickening of the Bowman's capsule and glomerular necrosis. These results show the importance of the 16/6 Id network in the induction and progression of SLE in mice.

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Induction of experimental systemic lupus erythematosus in mice by immunization with the F(ab')₂ fragment of the human anti-DNA monoclonal antibody carrying the 16/6 idiotype.

Ruiz PJ, Zinger H, Mozes E.

Department of Chemical Immunology, Weizmann Institute of Science, Rehovot, Israel.

Induction of an experimental disease resembling murine systemic lupus erythematosus (SLE), has been achieved in mice by immunization with a human monoclonal anti-DNA antibody, bearing a common idiotype, designated 16/6 Id. In the present study we report the preparation of F(ab')₂ proteolytic fragments of the human 16/6 Id mAb and the ability of the latter to induce experimental-SLE in mice. Following immunization with the F(ab) fragment, mice developed antibodies bearing the 16/6 Id, anti-16/6 Id and a variety of autoantibodies, similar to mice immunized with the whole 16/6 Id molecule. Serological manifestations of the disease such as leukopenia, proteinuria and renal damage, were developed following the immunization with the 16/6 Id F(ab')₂ proteolytic fragments. These results demonstrate the pathogenic role of the F(ab')₂ fragment that bears the 16/6 Id.

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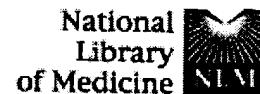
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